

We claim:

- 5 1. A method of sensing a signal from an oscillating bioNEMs transducer comprising:
  - generating an output signal from the oscillation of the transducer;
  - mixing the output signal with a reference signal;
  - filtering the mixed output signal to generate a correlator output,  $r(t)$ ;
  - 10 detecting the correlator output to generate a signal  $u(t)$ ;
  - determining whether the signal  $u(t)$  satisfies a predetermined threshold; and
  - deciding whether the signal  $u(t)$  represents a predetermined type of interaction between a free ligand in a fluid and a receptor attached to the transducer.
- 15 2. The method of claim 1 where determining whether the signal  $u(t)$  satisfies a predetermined threshold comprises applying the Neyman-Pearson criterion based on a predetermined probability of false detection,  $P_{fa}$ .
- 20 3. The method of claim 1 where determining whether the signal  $u(t)$  satisfies a predetermined threshold comprises determining whether a likelihood ratio of probability density functions of bound and unbound configurations of the ligand and receptor has a predetermined value.

4. The method of claim 1 where deciding whether the signal  $u(t)$  represents an predetermined type of interaction between a free ligand in a fluid and a receptor attached to the transducer comprises deciding based on  $u(t)$  whether the ligand has bound to the receptor.
- 5 5. The method of claim 1 where deciding whether the signal  $u(t)$  represents an predetermined type of interaction between a free ligand in a fluid and a receptor attached to the transducer comprises deciding based on  $u(t)$  whether a bound ligand has been released from the receptor by competitive binding with the free ligand.
6. The method of claim 1 where detecting the correlator output to generate a signal  
10  $u(t)$  comprises squaring the signal,  $r(t)$ .
7. The method of claim 1 where detecting the correlator output to generate a signal  $u(t)$  comprises detecting the envelope of the signal,  $r(t)$ .
8. The method of claim 1 further comprising sampling a plurality of measurements of the signal,  $u(t)$  and summing the sample signals to generate a signal,  $q(t)$ , which is  
15 then tested for qualification relative to a threshold and from which qualified signals a decision is made as to the interaction which as occurred between the free ligand and receptor.
9. A method of sensing a signal from an oscillating bioNEMs transducer comprising:

generating an output signal from the oscillation of the transducer;  
chopping the output signal in time;  
filtering the mixed output signal to generate a correlator output,  $r(t)$ ;  
generating summed and differenced quadrature components of the filtered

5 chopped signal;

multiplying the summed and differenced quadrature components to generate a  
signal,  $z(t)$ ;

integrating  $z(t)$  over a sample period,  $T$ , to generate a signal,  $u(t)$ ;

summing multiple measurements of  $z(t)$  over  $N$  sample periods to generate a  
10 signal,  $q(t)$ ;

determining whether the signal  $u(t)$  satisfies a predetermined threshold; and

deciding whether the signal  $u(t)$  represents an predetermined type of interaction  
between a free ligand in a fluid and a receptor attached to the transducer.

10. The method of claim 9 where determining whether the signal  $u(t)$  satisfies a  
15 predetermined threshold comprises applying the Neyman-Pearson criterion based on a  
predetermined probability of false detection,  $P_{fa}$ .

11. The method of claim 9 where determining whether the signal  $u(t)$  satisfies a  
predetermined threshold comprises determining whether a likelihood ratio of probability  
density functions of bound and unbound configurations of the ligand and receptor has a  
20 predetermined value.

12. The method of claim 9 where deciding whether the signal  $u(t)$  represents an predetermined type of interaction between a free ligand in a fluid and a receptor attached to the transducer comprises deciding based on  $u(t)$  whether the ligand has bound to the receptor.

5 13. The method of claim 9 where deciding whether the signal  $u(t)$  represents an predetermined type of interaction between a free ligand in a fluid and a receptor attached to the transducer comprises deciding based on  $u(t)$  whether a bound ligand has been released from the receptor by competitive binding with the free ligand.

14. The method of claim 1 further comprising:

10 providing the NEMS transducer with an attached bioreceptor;

exposing the biofunctionalized transducer to a free ligand in fluid;

interacting the free ligand with the bioreceptor to provide an interaction therebetween; and

oscillating the transducer to detect the existence of the interaction between the  
15 bioreceptor and free ligand.

15. The method of claim 1 where generating a output signal from the oscillation of the transducer comprises oscillating a piezoresistive transducer by means of thermal fluctuations.

16. The method of claim 1 where generating a output signal from the oscillation of the transducer comprises oscillating a piezoresistive transducer by means of a driving signal.

17. The method of claim 1 where generating a output signal from the oscillation of the transducer comprises oscillating a piezoresistive transducer by means of oscillating a coupled second transducer.

18. The method of claim 17 where oscillating a piezoresistive transducer by means of oscillating a coupled second transducer comprises coupling the piezoresistive transducer with the second transducer by fluid coupling therebetween.

19. The method of claim 17 where oscillating a piezoresistive transducer by means of oscillating a coupled second transducer comprises coupling the piezoresistive transducer with the second transducer by ligand coupling therebetween.

20. The method of claim 1 further comprising providing a substrate and ligand coupling the transducer to the substrate.

21. An apparatus for sensing an output signal from an oscillating bioNEMs transducer comprising:

mixing means coupled to the transducer for mixing the output signal with a reference signal;

filtering means coupled to the mixing means for filtering the mixed output signal to generate a correlator output,  $r(t)$ ;

detector means coupled to the filtering means for detecting the correlator output to generate a signal  $u(t)$ ;

5 threshold means coupled to the detector means for determining whether the signal  $u(t)$  satisfies a predetermined threshold; and

decision means coupled to the threshold means for deciding whether the signal  $u(t)$  represents a predetermined type of interaction between a free ligand in a fluid and a receptor attached to the transducer.

10 22. The apparatus of claim 21 where the threshold means comprises means for applying the Neyman-Pearson criterion based on a predetermined probability of false detection,  $P_{fa}$ .

23. The apparatus of claim 21 where the threshold means for determining whether a likelihood ratio of probability density functions of bound and unbound configurations of  
15 the ligand and receptor has a predetermined value.

24. The apparatus of claim 21 where decision means comprises means for deciding based on  $u(t)$  whether the ligand has bound to the receptor.

25. The apparatus of claim 21 where the decision means comprises means for deciding based on  $u(t)$  whether a bound ligand has been released from the receptor by  
20 competitive binding with the free ligand.

26. The apparatus of claim 21 where the detector means comprises means for squaring the signal,  $r(t)$ .

27. The apparatus of claim 21 where the detector means comprises means for detecting the envelope of the signal,  $r(t)$ .

5 28. The apparatus of claim 21 further comprising sampling means coupled to the detector means for sampling a plurality of measurements of the signal,  $u(t)$  and integration means for summing the sample signals to generate a signal,  $q(t)$ , which is then tested for qualification relative to a threshold and from which qualified signals a decision is made as to the interaction which as occurred between the free ligand and  
10 receptor.

29. An apparatus for sensing an output signal from an oscillating bioNEMs transducer comprising:

chopper means coupled to the transducer for chopping the output signal in time;

filtering means coupled to the chopper means for filtering the mixed output signal

15 to generate a correlator output,  $r(t)$ ;

quadrature means coupled to the filtering means for generating summed and differenced quadrature components of the filtered chopped signal;

mixing means coupled to the quadrature means for multiplying the summed and differenced quadrature components to generate a signal,  $z(t)$ ;

20 integration means coupled to the mixing means for integrating  $z(t)$  over a sample period,  $T$ , to generate a signal,  $u(t)$ ;

summing means coupled to the integration means for summing multiple measurements of  $z(t)$  over  $N$  sample periods to generate a signal,  $q(t)$ ;

threshold means coupled to the summing means for determining whether the signal  $u(t)$  satisfies a predetermined threshold; and

5        decision means coupled to the threshold means for deciding whether the signal  $u(t)$  represents an predetermined type of interaction between a free ligand in a fluid and a receptor attached to the transducer.

30.    The apparatus of claim 29 where the threshold means comprises means for applying the Neyman-Pearson criterion based on a predetermined probability of false  
10    detection,  $P_{fa}$ .

31.    The apparatus of claim 29 where the threshold means comprises means for determining whether a likelihood ratio of probability density functions of bound and unbound configurations of the ligand and receptor has a predetermined value.

32.    The apparatus of claim 29 where the decision means comprises means for  
15    deciding based on  $u(t)$  whether the ligand has bound to the receptor.

33.    The apparatus of claim 29 where the decision means comprises means for deciding based on  $u(t)$  whether a bound ligand has been released from the receptor by competitive binding with the free ligand.



34. The apparatus of claim 21 where the NEMS transducer has an attached bioreceptor which is biofunctionalized to a free ligand in fluid, such that interaction of the free ligand with the bioreceptor is detected by an effect on the oscillation of the transducer.

5 35. The apparatus of claim 21 further comprising means for generating a output signal from the oscillation of the transducer which means comprises a piezoresistive transducer oscillated by means of thermal fluctuations.

36. The apparatus of claim 21 further comprising means for generating a output signal from the oscillation of the transducer which means comprises a piezoresistive  
10 transducer oscillated by means of an external driving signal.

37. The apparatus of claim 21 further comprising means for generating a output signal from the oscillation of the transducer which means comprises a piezoresistive transducer oscillated by means of an oscillating coupled second transducer.

38. The apparatus of claim 37 where the piezoresistive transducer is oscillated by  
15 means of fluid coupling with the second transducer.

39. The apparatus of claim 37 where the piezoresistive transducer is oscillated by means of ligand coupling with the second transducer.

40. The apparatus of claim 21 further comprising a substrate which is ligand coupled to the transducer.